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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,979	03/07/2001	Masayuki Fukumura	4001-0003	8941

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EXAMINER
KATCHEVES, KONSTANTINA T

ART UNIT	PAPER NUMBER
1636	20

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,979	FUKUMURA ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5, 16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-15 are pending in the instant application. The present Office Action is in response to Paper No. 19, filed 01 November 2002.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 19 is acknowledged. Claims 11 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 19. Accordingly, claims 1-10 and 13-15 are currently underexamination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 and 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 9 of copending Application No. 09/070938. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention of the instant claims would have been obvious to one of ordinary skill in the art. The instant claims are drawn to a method for transferring nucleic acid into nerve cells and a negative sense RNA viral vector, more specifically a sendai viral vector, for transferring nucleic acid inot a nerve cell. The claims of the '938 application are drawn to an RNA construct derived from Sendai virus and host cell comprising said construct. The RNA construct of the '938 application is a species that anticipates the negative sense RNA viral vector. Given that the claims in the '938 application are also drawn to a host cell comprising the construct, the method of the claims in the instant application would have been obvious to one of skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-7 and 13-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 09/762641. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the invention of the instant claims would have been obvious to one of ordinary skill in the art. As discussed above, the instant claims are drawn to a method for transferring nucleic acid into nerve cells and a negative sense RNA viral vector, more specifically a sendai viral vector, for transferring nucleic acid inot a nerve cell. The claims of the '641 application are drawn to an RNA construct derived from Sendai virus and a method for expressing a foreign gene. As above, the RNA construct of the '641 application is a species that anticipates the negative sense RNA viral vector. Given that the claims in the '641 application are also drawn to a method using the RNA construct, the method of the claims in the instant application would have been obvious to one of skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Specification

The disclosure is objected to because of the following informalities: The specification on page 18, line 29 and page 19, line 25 recite the range "38° C to 38° C." This is not a range, rather is a precise temperature. The sentence on page 19, line 29 is grammatically incorrect. It is not clear what meaning of the phrase "brain region containing were made into" really is.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-10 and 13-15 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description requirement is established by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Applicant's claims are drawn to a broad genus of viruses, a negative sense RNA viral vector. These are genus claims that encompass a wide array of virus. The specification, however, merely discloses one such virus, Sendai virus (SeV). Moreover, Applicant fails to disclose what genes or components of Sendai virus are required to function as a viral vector for the transfer of genetic material to nerve cells. Applicant does not disclose any of the variants or modifications embraced by such a broad genus of viral vectors. Thus, the specification does not describe the complete structure of a representative number of species. Absent such teachings and guidance, as to the structure-function relationship of this genus of vectors, the specification does not describe the claimed recombinant DNA molecules in such full, clear, concise and exact terms so as to indicate that Applicant had possession of these molecules at the time of filing of the present application. Additionally, the vector encodes a secretory protein. This is also a

broad genus and Applicant fails to have possession of all secretory proteins embraced by the breadth of the claims for the reasons discussed. In other words, Applicant has failed to described the characteristics of the negative sense RNA viruses embraced by the invention that make it a vector that capable of transferring nucleic acids into nerve cells and capable of expressing proteins that are capable of protecting the brain from ischemia. Thus, the written description requirement has not been satisfied.

Claims 1-10 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vivo* methods for gene therapy in rats and mice, does not reasonably provide enablement for *in vivo* methods in other organisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Although each of the above factors has been considered, those most relevant to the instant rejection are discussed in detail below. Applicant's invention of the instant claims is drawn to method for the transfer of nucleic acids into nerve cells. The transfer of heterologous genes is used a means of protecting the brain from ischemia. Methods of targeting nucleic acids into host cells *in vivo* fall into the broad area of gene therapy. Successful gene therapy methods are based, fundamentally, upon the ability to deliver exogenous nucleic acids to cells or tissues of interest.

Despite experimentation a tremendous amount of effort by skilled artisans in the field of gene delivery and expression *in vivo*, there remain significant hurdles known in the art to make and use the invention over the scope claimed. Anderson (Nature Vol. 392, supp 1998) reports that progress in developing effective gene therapy is slow. Anderson further states, "the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. . . . [the] goal is more diffuclt to achieve than many investigators had predicted. . . [the] human body has spent many thousands of years learning to protect itself. . ." See page 25, column 1.

Verma et al. (Nature Vol. 389 1997), and Palu et al. (J. of Biotech. Vol.68 1999) also discuss the inherent difficulties transfecting cells *in vivo* by targeted delivery mechanisms. Transferred genes can be induced to function in a whole animal; however, no approach has been fully successful for *in vivo* gene transfer. See Verma page 239. Moreover, the main obstacle to

the development of gene therapy is the targeted long-term expression of the transgene. The *in vivo* transfection of cells has not been fully successful for many reasons including the complexity the biological systems of living organisms, the inability of the genes to reach enough of the target cells, and the inability of the genes to function properly or for a significant period of time even if they do reach the cells. See Palu page 10 and Anderson page 25.

The inabilities to target viral vectors effectively and express them efficiently are not the only hurdles facing gene therapy. Another major obstacle is the unpredictable nature of gene therapy when one tries to extrapolate from animal models to human systems. Crystal (Science Vol. 270 1995) provides a long list of clinical trials that have yet to yield therapeutic benefits and further states that "humans are not simply large mice." See page 409. While the usefulnesness of gene therapy is recognized, these references indicate that there are numerous obstacles to successful gene therapy, which current methods still must overcome. The specification discloses examples where nerve cells are transformed in culture and provide examples were an SeV vector was stereotactically administered to mouse and rat brains. Applicant discloses that in order "to examine SeV infection of pyramidal cells of the hippocampus, which is the main object of the invention precisely targeted administration of SeV to the vicinity of the hippocampus is required."

Emphasizing the point disclosed by Crystal, Gura (Science Vol.278 1997) quotes: "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." Gura states that they had "basically discovered compounds that were good mouse drugs rather than good human drugs." See page 1041. Thus, even though those of skill in the art have

used mouse models, their use does not necessarily connote efficacy in other subjects such as humans.

Upon examination of Applicant's disclosure, no evidence or data is apparent that the vector will reasonably reach its target location, deliver the DNA to the target cell in an amount sufficient for successful gene therapy in any subject. Without further evidence, Applicant has not overcome the state of the art in his specification and is not enabled for *in vivo* methods of transforming cells in subjects other than rats and mice. Considering the inherent difficulties in the art, Applicant's disclosure does not teach how to overcome those obstacles such that the invention will do what Applicant asserts it will do.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear whether claim one is drawn to a method or inappropriately to a method and a product. Is the claim drawn to a method either comprising a step wherein nerves cells are contacting a negative-sense RNA viral vector or comprising a step wherein a nerve cells are contacted to transformed cells. Alternatively, the claim drawn to a method comprising contacting a negative-sense RNA viral vector to a nerve cell or to cells comprising said vector. This ambiguity renders the claim vague and indefinite.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (703) 305-1999. The examiner can normally be reached on Monday through Friday 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3388.

Konstantina Katcheves
January 10, 2003

Gerald G. Leffers Jr.
PATENT EXAMINER
Gerald G. Leffers Jr
A.U. 1636